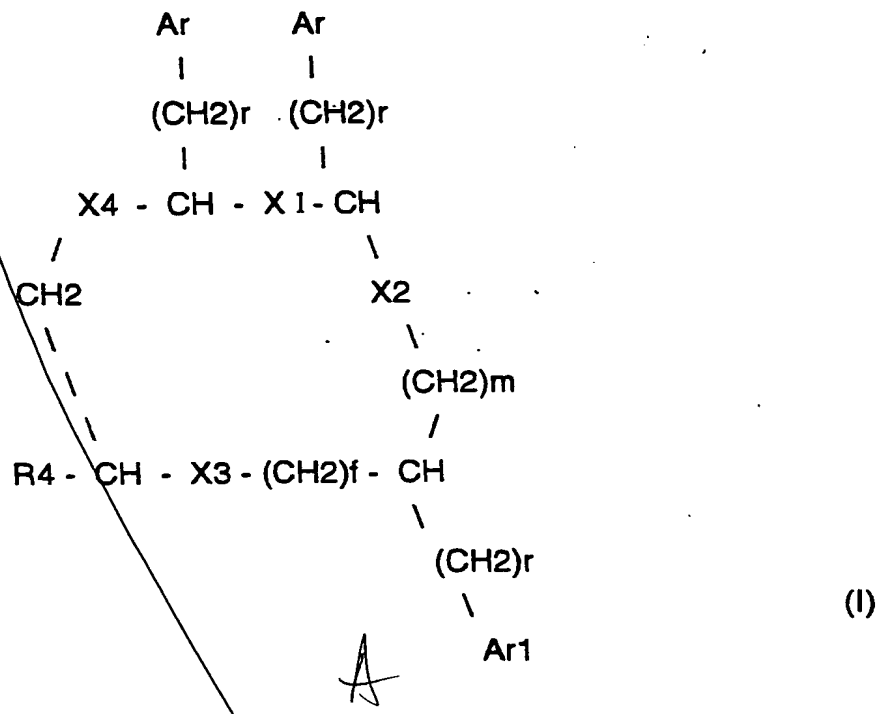
CLAIMS

1. Monocyclic compounds of general formula (I)



(I)

wherein:

X_1, X_2, X_3, X_4, same or different, are a group chosen among: -CONR-, -NRCO-, $-CH_2-NR-$, $-NR-CH_2-$ where R is H, C_{1-3} alkyl, benzyl;

f, m, same or different, are a number chosen among 0,1 and 2;

R_1 and R_2, same or different, represent a group:

$-(CH_2)_r$ -Ar where r = 0, 1, 2 and Ar is an aromatic group chosen among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 substituents chosen among C_{1-3} alkyl, haloalkyl, C_{1-3} alkyoxy, C_{2-4} amino-alkyoxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 ed R_7, same or different, are H or C_{1-3} alkyl,

R_3 is

$(CH_2)_r$-Ar_1 where r = 0, 1, 2 and Ar_1 is an aromatic group chosen among: benzene, naphtalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole,

possibly substituted with up to 2 groups chosen among C_{1-3} alkyl and haloalkyl, C_{1-3} alkyoxy and amino-alkyoxy, halogens, OH, NH_2, NR_6R_7, where R_6 and R_7,

← -alkyloxy, halogens, OH, NH_2,

same or different, are H or C_{1-3} alkyl,

R_4 is a group chosen among:

- NR_8R_9, where R_8 is H or C_{1-3} alkyl and

R_9 is

(i) a methanesulfonyl, tosyl, tetrahydropyranyl,

(ii) tetrahydrothiopyranyl possibly mono or di-substituted by oxygen on the S atom,

(iii) piperidyl possibly substituted on the N-atom by a C_{1-3} alkyl, C1-3 acyl, aminosulfonyl, methanesulfonyl;

(iv) a group $(CH2)g-R_{10}$ where g is 1,2,3 and R_{10} is chosen among morpholine, furan, CN;

or R_8 and R_9 together with the N atom to which they are linked form a piperazine possibly substituted on one of its nitrogen by a C_{1-3} alkyl, C1-3 acyl o methanesulfonyl;

$N(R_{11})CO(CH_2)h-R_{12}$ where R_{11} is H C_{1-3} alkyl; h is 0,1,2,3; and R_{12} is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or hydroxymethyl, piperidine possibly substituted with a group hydroxy carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophéne, thiomorpholine possibly mono or di-oxygenated on the S-atom, amino- cyclohexane possibly substituted by an hydroxy group.

- COR_{13} wherein R_{13} is a group chosen among morpholine and piperazine possibly substituted by a C_{2-6} alkyl containing one or more ether or hydroxy groups;

as enantiomers or mixture of diastereoisomers, and their pharmaceutically accepatble salts.

2. Compound according to Claim 1 wherein:

f is 1

m is 0

X_1, X_2, X_3, X_4, same or different are a group -CONR- and -NRCO-,

R is H or methyl

R_1 and R_2 same or different, are:

$-CH_2$-Ar wherein Ar is an aromatic group chosen among benzene, pyridine, indole, possibly substituted up to two residues with substituents chosen among: C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino alkyloxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl;

R_3 is

- CH_2-Ar_1 wherein Ar_1 is an aromatic group chosen among: alfa naphthyl, beta naphthyl, phenyl, phenyl substituted up to two residues chosen among C_{1-3} alkyl and haloalkyl, C_{1-3} alkyloxy, halogens, OH, NH_2,

R_4 is as defined in Claim 1.

3. Compounds according to Claim 2 wherein:

- X_1, X_2, X_3, X_4 are -CONR-,

R is H

- R1 is the lateral chain of tryptophan;

- R2 is the lateral chain of phenylalanine possibly substituted with up to two residues chosen among: chlorine, fluorine, CF_3, OH, CN; or a group 3-pyridyl-methyl; or a group 4-pyridyl-methyl;

- R3 is benzyl.

and f, m and R_4 are as defined in claim 2

4.Compounds according to claim 3 wherein:

R, R1, R2, R3, f, m are as above defined and:

R4 is a group NR8R9 wherein:

R8 is H or methyl;

R9 is a group chosen among: : 4-tetrahydropyranyl, 4-tetrahydrothiopyranyl, 1-oxo-tetrahydrothiopyran-4-yl, 1,1-dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidinyl, N-metansulfonyl-4-piperidinyl, N-aminosulfonyl-4-piperidinyl,

or R8 and R9 together with the N atom to which they are linked represent: N-methyl-piperaziniyl, N-acetyl-piperazinyl, piperazinyl, N-methanesulfonyl-piperazinyl

5. Compounds according to Claim 4 represented by:

i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vi) cyclo{Suc[1-(R)-(1,1-dioxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vii) cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

viii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ix) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

x) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xi) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF3)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiv) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xv) cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvi) cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvii) cyclo{Suc[1-(R)-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xviii) cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xix) cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xx) cyclo{Suc[1-(R)-4-methanesulfonyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

6. Compound according to Claim 3 wherein :

R_4 represents a group NR_8R_9, where R_8 is H and R9 is chosen among: methanesulfonyl, tosyl, a group $(CH2)g-R_{10}$ wherein g is 1, 2 and R_{10} is chosen among: morpholine, furan, CN.

and f, m, X_1, X_2, X_3, X_4, R, R_1, R_2 and R_3 are as defined in claim 3

7. Compound according to claim 6 represented by:

xxi) cyclo{Suc[1-(S)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxii) cyclo{Suc[1-(R)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiii) cyclo{Suc[1-(S)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiv) cyclo{Suc[1-(R)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxv) cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvi) cyclo{Suc[1-(R)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvii) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxviii) cyclo{Suc[1-(R)-cianomethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-

$CH_2NH]\}$

8. Compounds according to claim 3 wherein:

R4 is a group $-N(R_{11})CO(CH_2)_h-R_{12}$ wherein R_{11} is H, h is 0 or 1, and R12 is chosen among: 1-tetrazolyl, 5-mercapto-tetrazol-1-yl, 1-triazolyl, furanyl, thiophenyl, morpholine, 4-hydroxy-piperidine, 4-carboxyamido-piperidine, 3-hydroxy-pyrrolidine, 2-hydroxymethylpyrrolidine, 4-methyl-piperazine, 4-aminosulfonyl-piperazine, 1-oxo-thiomorpholine, 4-hydroxy-cyclohexan-1-yl-amino and f, m, X_1, X_2, X_3, X_4, R, R_1, R_2 and R_3 are as defined in claim 3

9. Compounds according to Claim 8 represented by:

xxix) cyclo{Suc[1-(R)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxx) cyclo{Suc[1-(S)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxi) cyclo{Suc[1-(S)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxii) cyclo{Suc[1-(R)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxiii) cyclo{Suc[1-(S)-2-(5-mercapto-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxiv) cyclo{Suc[1-(R)-2-([1,2,4]triazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxv) cyclo{Suc[1-(R)-2-(furanil)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxvi) cyclo{Suc[1-(R)-2-(thiophen-3-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxvii) cyclo{Suc[1-(R)-(4-morpholino)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxviii) cyclo{Suc[1-(R)-2-(4-hydroxy-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxix) cyclo{Suc[1-(R)-2-(4-aminocarbonyl-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2

xl) cyclo{Suc[1-(R)-2-(3-hydroxy-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xli) cyclo{Suc[1-(R)-2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xliii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xliv) cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlv) cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlvi) cyclo{Suc[1-(R)-2-*(trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

10. Compounds according to Claim 3 wherein:

R4 represents a group COR_{13} wherein R_{13} is a group chosen among morpholine and 4-(hydroxyethyloxyethyl)-piperazine.

and f, m, X_1, X_2, X_3, X_4, R, R_1, R_2 and R_3 are as defined in claim 3

11. Compounds according to claim 10 represented by:

xlvii) cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlviii) cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

12. Pharmaceutical compositions containing as active principle compounds of general formula (I) according to Claim 1 in combination with pharmaceutically acceptable carriers or excipients.

13. Pharmaceutical compositions according to Claim 12 for use as tachykinins antagonists.

14. Pharmaceutical compositions according to claim 13 for use as antagonists on human NK2 receptor .

15. Pharmaceutical compositions according to claim 14 for use in the treatment of

the broncospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections, kidney colics.

16. Use of a compound according to Claim 1 as tachykinins antagonist

17. Use of a comound according to Claim 1 as NK-2 antagonist.

18. Use of a compound according to Claim 1 for the treatment of the broncospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections, kidney colics.

19.Method for the treatment of the broncospastic component of asthma, cough, pulmonary irritation, intestinal spasms or local spasms of bladder, uretere during cystitis, infections kidney colics wherein amounts of 0,1 - 10mg/ body weight of an active principle represented by compounds of formula (I) according to Claim 1 are administered to the patient.

Add A'

Add B'